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The Distribution of Fluoxetine and Norfluoxetine in Postmortem Fluids and Tissues

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16. Abstract

During aviation accident investigations, postmortem specimens from the flight crews are submitted to the Federal Aviation Administration's Civil Aerospace Medical Institute for toxicological analysis. Fluoxetine (Prozac) is a selective serotonin reuptake inhibitor that was introduced in 1986. Certain side effects of this medication — drowsiness, dizziness, abnormal vision, diarrhea, and headache — could affect pilot performance and become a factor in an aviation accident. Our laboratory has determined the distribution of fluoxetine and its desmethyl metabolite, norfluoxetine, in various postmortem tissues and fluids from 10 fatal aviation accident cases. When available, 11 specimen types were analyzed for each case, including: blood, urine, vitreous humor, bile, liver, kidney, skeletal muscle, lung, spleen, heart muscle, and brain. Specimens were extracted using solid-phase extraction and analyzed by GC/MS. Deuterated fluoxetine and norfluoxetine were used as internal standards to eliminate any possible matrix effects during extraction. Blood fluoxetine concentrations in these 10 cases ranged from 21 to 1480 ng/mL. Most cases fell within the expected therapeutic range for patients that regularly take this drug. The distribution coefficients for fluoxetine were determined to be: urine 0.9 ± 0.4, vitreous humor 0.10 ± 0.03, bile 9 ± 1, liver 38 ± 10, lung 60 ± 17, kidney 9 ± 3, spleen 20 ± 5, muscle 2.2 ± 0.3, brain 15 ± 3, and heart 10 ± 2. While the coefficient of variation (CV) for the distribution coefficients range from 11-44%, the distribution into heart, brain, muscle, spleen, and bile is relatively reproducible, each having a CV of ≤ 25%. To our knowledge, this is the first report presenting the distribution of fluoxetine in humans at therapeutic concentrations.

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INTRODUCTION

The Federal Aviation Administration's (FAA's) Civil Aerospace Medical Institute (CAMI) is responsible under Department of Transportation Orders 8020.11B and 1100.2C to "conduct toxicological analysis on specimens from … aircraft accident fatalities" and "investigate … general aviation and air carrier accidents and search for biomedical and clinical causes of the accidents, including evidence of … chemical [use]." Therefore, following an aviation accident, samples are collected at autopsy and sent to CAMI's Forensic Toxicology Research Laboratory where toxicological analysis is conducted on various postmortem fluids and tissues.

Fluoxetine, *N*-Methyl-γ-[4-(trifluoromethyl)phenoxy] benzenepropanamine, sold under the trade name Prozac, is a selective serotonin reuptake inhibitor (SSRI) that was introduced in 1986 by Ely Lilly.[1] According to the manufacturer, fluoxetine is the most widely prescribed medication in history for the treatment of depression, obsessive compulsive disorder (OCD), bulimia nervosa, premenstrual dysphoric disorder, and panic disorder.[1] Certain side effects of this medication, including drowsiness, dizziness, abnormal vision, diarrhea, and headache,[2, 3] could affect pilot performance and become a factor in an aviation accident. Therefore, the use of this medication by pilots is not permitted by the FAA.

Fluoxetine is slowly absorbed following oral administration. Peak plasma concentrations typically occur within 4-8 hours of consumption, and the half-life has been reported to be approximately 4 days.[4] Fluoxetine is metabolized in the body to the active desmethyl metabolite, norfluoxetine. The chemical structures of these two compounds can be seen in Figure 1.

A limited amount of scientific information concerning the distribution of fluoxetine has been reported.[2, 5, 6] Additionally, none of the data pertains to therapeutic levels. Since scientific information concerning the distribution of fluoxetine at therapeutic levels is not available, our laboratory set out to determine its distribution in various postmortem tissues and fluids. A search of our laboratory database identified ten aviation fatalities that were reported positive for fluoxetine and norfluoxetine in blood and also had a full complement of biological tissues and fluids available for analysis. These specimens types included urine, vitreous humor, bile, skeletal muscle, liver, kidney, lung, spleen, brain, and heart muscle. This manuscript presents the quantitation and distribution of fluoxetine and norfluoxetine in postmortem specimens and identifies specimen types that may be suitable for estimating blood concentrations of fluoxetine in the event that blood is unavailable for analysis.

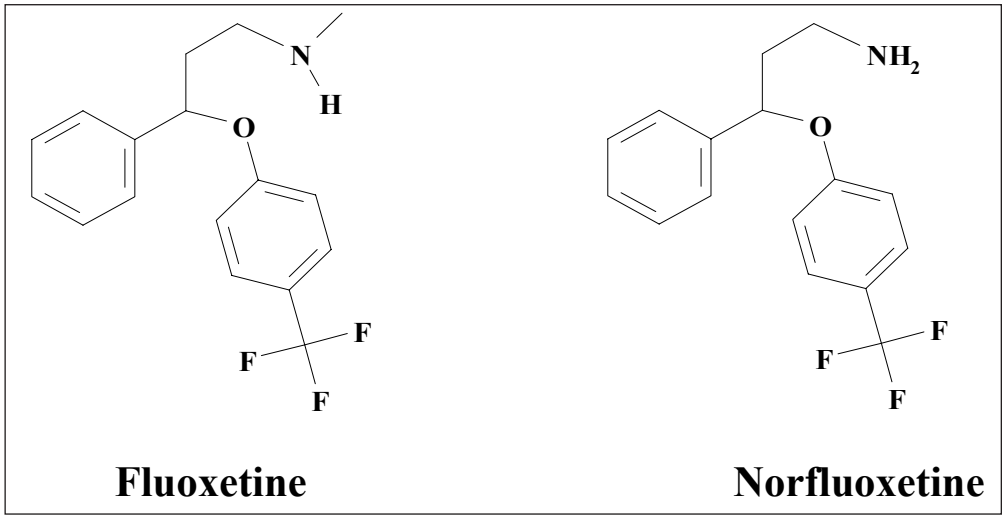

Figure 1. Chemical structures of fluoxetine and norfluoxetine.

MATERIALS AND METHODS

Chemicals and Reagents

All aqueous solutions were prepared using double deionized water (DDW), which was obtained using a Milli-QT_{plus} Ultra-Pure Reagent Water System (Millipore®, Continental Water Systems, El Paso, TX). All chemicals described below were purchased in the highest possible purity and used without any further purification. Fluoxetine and norfluoxetine were purchased from Cerilliant (Cerilliant Corp., Round Rock, TX) as methanolic standards at a concentration of 1.00 mg/mL in sealed glass ampules. Fluoxetine-d_6, and norfluoxetine-d_6 were purchased from Cerilliant as methanolic standards at a concentration of 0.100 mg/mL in sealed glass ampules. The derivatization reagent, pentafluoropropionic anhydride (PFPA), was obtained from Pierce (Pierce Inc., Rockford, IL, USA). Methanol, acetonitrile, ammonium hydroxide, acetic acid, ethyl acetate, sodium fluoride, and potassium phosphate monobasic were purchased from Fisher Scientific (Pittsburgh, PA). The pH of all solutions was measured using a Corning model 430 pH meter (Corning Life Sciences, Acton, MA) connected to a Corning 3-in-1 model pH electrode.

Gas Chromatographic/Mass Spectroscopic Conditions

All analyses were performed using a bench-top gas chromatograph/mass spectrometer (GC/MS), which consisted of a Hewlett Packard (HP) 6890 series GC, interfaced with a HP 5973 quadrupole MS (Agilent, Palo Alto, CA). The GC/MS was operated with a transfer line temperature of 280°C and a source temperature of 250°C. The MS was tuned on a daily basis using perfluorotributylamine. The electron multiplier voltage was set at 106 eV above the tune value. Chromatographic separation was achieved using a Varian FactorFour® crosslinked 100% methyl siloxane capillary column 12 m x 0.2 mm i.d., 0.33 µm film thickness (Varian Co., Harbor City, CA.). Helium was employed as the carrier gas and used at a flow rate of 1.0 mL/min. An HP 6890 autosampler was used to inject 1 µL of extract into the GC/MS. The GC was equipped with a split/splitless injection port operated at 250°C in the splitless mode with the purge time of 0.5 min. The oven temperature profile was established as follows: 70°C – 290°C at 30°C/min and a final hold time of 2.67 min, resulting in a total run time of 10 min. Initially, neat standards of each compound (1 µL of a 100 ng/µL solution) were injected individually and analyzed using the full scan mode of the GC/MS, which scanned from 50 to 600 AMU. Quantitation and qualifier ions for each analyte were then selected based on both abundance and mass-to-charge ratio (*m/z*). To increase reproducibility and reduce interference, high mass ions were selected when possible. The ions chosen for each respective analyte can be seen in Table 1. Upon selection of unique ions, the MS was run in selected ion monitoring (SIM) mode with a dwell time of 30 msec for each recorded ion.

Sample Selection and Storage

A search of the CAMI database identified 10 fluoxetine-positive fatalities from separate civil aviation accidents from the previous 5 years that had a majority of the desired biological tissues and fluids (blood, urine, vitreous humor, bile, liver, kidney, muscle, lung, spleen, heart, and brain) available for analysis. In all cases, blood was stored at -20°C in tubes containing 1.00% (w/v) sodium fluoride/potassium oxalate until analysis. All other specimens were stored without preservation at -20°C until analysis. Blood fluoxetine and norfluoxetine concentrations determined in this study agreed well with those previously determined by our laboratory via this analytical method. All concentrations found were within 10% of the value originally determined, verifying that no deterioration in either fluoxetine or norfluoxetine concentration had occurred during storage.

Calibrator and Control Preparation

Calibration curves for both fluoxetine and norfluoxetine were prepared by serial dilution utilizing bovine whole blood as the diluent. Calibrators were prepared

Table 1. Ions utilized for the quantitation of fluoxetine and norfluoxetine.

Compound	Ions utilized for quantitation (*m/z*)*
Fluoxetine	**294**, 115, 117
Norfluoxetine	**280**, 117, 115
Fluoxetine-d_6	**300**, 123, 301
Norfluoxetine-d_6	**286**, 123, 110

***** Ions in bold used for quantitation, other ions used as qualifiers.

from one set of original stock standard solutions, while controls were prepared in a similar manner as calibrators, using bovine whole blood as the diluent, but from a second set of unique stock solutions. Calibration curves were prepared at concentrations ranging from 1.56 – 800 ng/mL. A minimum of 7 calibrators were used to construct each calibration curve. Controls were prepared at concentrations of 80 and 320 ng/mL and extracted with each batch of unknowns to verify the accuracy of the calibration curve. The internal standard solution, containing fluoxetine-d_6 and norfluoxetine-d_6, was prepared at a concentration of 400 ng/mL in DDW by dilution from the stock standard of each compound.

Quantitation was achieved via an internal standard calibration procedure. Response ratios for each compound were determined for every sample analyzed. The response ratio was calculated by dividing the area of the analyte peak by the area of the internal standard peak. Calibration curves were derived by plotting a linear regression of the analyte/internal standard response ratio versus the analyte concentration for each respective calibrator. These calibration curves were then used to determine the concentrations of each compound in the prepared controls and biological specimens.

Sample Preparation and Extraction Procedure

Postmortem specimens, calibrators, and controls were extracted in the following manner. Tissue specimens were homogenized using an Omni post-mounted homogenizer (Omni Int., Marietta, GA). The generator used with this homogenizer was 30 mm in diameter and set to rotate at 22,000 rpm. Tissues were homogenized following a 1:2 dilution with 1.00% NaF in DDW. Three mL aliquots of postmortem fluid, calibrator, and control, and 3.00 g aliquots of each tissue homogenate (1.0 g tissue) were transferred to individual 16 x 150 mm screw-top tubes. To each specimen, calibrator, and control, 1.00 mL of the internal standard mixture (400 ng) was added. Samples were vortexed briefly and allowed to stand at room temperature for 10 min. Nine mL ice-cold acetonitrile was added to each sample. The mixture was then placed on a rotary mixing wheel and mixed for 15 min by simple rotation of the wheel at 15 rpm. Centrifugation at 820×*g* for 5 min removed cellular debris and proteins. Following centrifugation, the supernatant was transferred to clean 16 x 125 mm culture tubes and evaporated in a TurboVap® Concentration Workstation at 40°C (Caliper Life Sciences, Hopkinton, MA) under a stream of dry nitrogen to a volume of approximately 1 mL. Following acetonitrile evaporation, 4.00 mL 0.10 M phosphate buffer, pH 6.00 was added to each sample. The extracts were transferred to Bond Elute Certify® solid-phase extraction (SPE) columns obtained from Varian (Varian Co., Harbor City, CA.), which had been pre-conditioned with 2.00 mL methanol, followed by 2.00 mL 0.10 M phosphate buffer, pH 6.00. Care was taken not to dry the column prior to loading sample. Column flow rates of 1-2 mL/min were maintained in each SPE step using a Varian 24 port Cerex™ SPE processor (Varian Co., Harbor City, CA.) with a nitrogen pressure of 3 psi. Once each sample had passed through its respective column, the columns were washed with 1.00 mL of 1.00 M acetic acid then dried completely with 25 psi nitrogen for 5 min. The columns were again washed by adding 6.00 mL methanol to each. Following the methanol wash, the columns were again dried completely with 25 psi nitrogen for 5 min. The analytes were eluted off the columns with 3.00 mL of 2.00% ammonium hydroxide in ethyl acetate, which was prepared fresh daily. Eluents were evaporated to dryness in a TurboVap® set at 40°C under a stream of dry nitrogen. Derivatization of these compounds was advantageous because each compound contained a polar functional group that could be replaced to produce a less polar compound with higher mass ions for GC/MS analysis. Derivatization was accomplished by adding 50 µL of ethyl acetate, followed by 50 µL of pentafluoropropionic anhydride (PFPA) to each specimen. The samples were then capped tightly, vortexed, and incubated at 70°C for 20 min. Following derivatization, the tubes were allowed to cool to room temperature, and the contents were evaporated to dryness in a TurboVap® set at 40°C. Once dry, the contents of each tube were reconstituted in 50 µL of ethyl acetate and transferred to GC/MS vials for analysis.

RESULTS AND DISCUSSION

Analysis of Fluoxetine and Norfluoxetine

The procedure described herein, which utilizes SPE and GC/MS for the detection of the PFPA derivatives of both fluoxetine and norfluoxetine, is rapid, reproducible, and sensitive. Analyte peaks were completely resolved, and each provided quantitation ions with unique *m/z*, so no interference was observed. Deuterated fluoxetine and norfluoxetine were used as internal standards for this study. This eliminated any concerns over possible matrix effects and allowed for accurate quantitation in specimen types other than blood while using a blood calibration curve. No analyte suffered interference from endogenous/exogenous matrix components.

The mass spectra of fluoxetine, norfluoxetine, fluoxetine-d_6, and norfluoxetine-d_6 each provided numerous high mass ions. Quantitation and qualifier ions for each compound are shown in Table 1. Acceptability criteria employed for analyte identification and quantitation were as follows: 1) ion ratios for a given analyte, measured as

the peak area of a qualifier ion divided by the peak area of the quantitation ion, were required to be within ± 20% of the average of the ion ratios for each respective calibrator used to construct the calibration curve for that analyte; 2) each ion monitored was required to have a minimum signal-to-noise ratio (S/N) of 10; and 3) the analyte was required to have a retention time within ± 2.00% of the average retention time for each respective calibrator used to construct the calibration curve for that analyte. Analytes not meeting these criteria were reported as either negative or inconclusive.

The linear dynamic range (LDR), limit of detection (LOD), and limit of quantitation (LOQ) for both fluoxetine and norfluoxetine were determined using whole blood as the matrix. The LDR for each analyte was determined to be 3.13 – 800 ng/mL. Correlation coefficients for calibration curves used to ascertain the LDR were greater than 0.994 when a weighting factor of 1/X was employed. The LOD was defined as the lowest analyte concentration detectable that met the above-discussed identification criteria. The LOQ was defined as the lowest analyte concentration detectable that not only met all identification criteria discussed above but also had an experimentally determined concentration within ± 20% of its prepared value. The LOD for both fluoxetine and norfluoxetine was determined to be 1.56 ng/mL. The LOQ for these two compounds was determined to be 3.13 ng/mL.

Carryover was not found to be a problem on the GC/MS; however, it was initially investigated and subsequently monitored by the use of ethyl acetate blank injections. The injection of an ethyl acetate blank following the 800 ng/mL calibrator showed no carryover contamination. Subsequently, ethyl acetate blanks were utilized between each postmortem specimen throughout the sample sequence to verify that no sample-to-sample contamination had occurred.

Postmortem Concentrations of Fluoxetine and Norfluoxetine

Blood concentrations found in the ten cases examined ranged from 0.021 to 1.48 µg/mL. Therapeutic levels of fluoxetine, in serum, range from 0.150 to 0.500 µg/mL.[4] Assuming the blood/serum distribution ratio is 1:1 (the blood/serum distribution ratio is not available in published literature), blood concentrations in these cases ranged from slightly below therapeutic to slightly above it. The concentration of these compounds in each postmortem specimen from these 10 cases can be seen in Tables 2-3. With a relatively large volume of distribution (20-42 L/kg), fluoxetine was expected to be found at high concentrations in the tissue specimens analyzed. As can be seen in Tables 2-3, this was the case. The following mean concentrations (µg/mL, µg/g) of fluoxetine were found: blood 0.430 (range 0.021-1.48, *n*=10), urine 0.208 (0.025-0.385, *n*=5), vitreous humor 0.022 (0.005-0.038, *n*=3), bile 3.51 (0.126-5.90, *n*=8), liver 11.3 (0.691-28.6, *n*=8), lung 19.6 (1.56-51.9, *n*=8), kidney 3.01 (0.204-8.72, *n*=10), spleen 6.83 (0.361-18.4, *n*=10), muscle 1.04 (0.046-2.48, *n*=8), brain 4.64 (0.316-10.3, *n*=9), heart 3.98 (0.227-8.26, *n*=9). The following mean concentrations (µg/mL, µg/g) of norfluoxetine were found: blood 0.410 (range 0.054-0.879, *n*=10), urine 0.322 (0.175-0.754, *n*=5), vitreous humor 0.024 (0.018-0.031, *n*=3), bile 3.17 (0.783-4.44, *n*=8), liver 16.83 (5.83-28.0, *n*=8), lung 25.3 (7.38-37.9, *n*=8), kidney 3.53 (1.02-5.78, *n*=10), spleen 8.26 (2.78-12.2, *n*=10), muscle 0.881 (0.337-1.59, *n*=8), brain 7.24 (2.32-11.3, *n*=9), heart 2.85 (1.54-4.08, *n*=9).

The distribution coefficients for both fluoxetine and norfluoxetine, expressed as specimen/blood ratios, are summarized in Tables 4-5. The distribution coefficients for fluoxetine were determined to be: urine 0.9 ± 0.4, vitreous humor 0.10 ± 0.03, bile 9 ± 1, liver 38 ± 10, lung 60 ± 17, kidney 9 ± 3, spleen 20 ± 5, muscle 2.2 ± 0.3, brain 15 ± 3, heart 10 ± 2. The distribution coefficients for norfluoxetine were determined to be: urine 0.8 ± 0.3, vitreous humor 0.07 ± 0.02, bile 7 ± 1, liver 42 ± 13, lung 59 ± 17, kidney 9 ± 2, spleen 21 ± 6, muscle 2.0 ± 0.4, brain 18 ± 3, heart 7 ± 2.

As can be seen, fluoxetine distribution coefficients for urine, bile, vitreous humor, muscle, kidney, lung, spleen, brain, liver, and heart had coefficient of variation (CV) values between 11 and 44%. Norfluoxetine distribution coefficients for these same specimens had CV values between 14 and 38%. It is widely accepted that basic drugs with large volumes of distribution can undergo postmortem redistribution. This redistribution may account for some of the larger CVs. However, the relatively small CVs suggest that postmortem redistribution may not have been a significant factor in any of these cases.

Drug concentrations in blood may aid in determining impairment and/or cause of death. However, our laboratory received blood in only approximately 70% of our cases. There are no widely accepted criteria for what constitutes an acceptable distribution coefficient; however, it may be possible, with caution, to use a tissue or fluid distribution coefficient to crudely estimate a blood concentration in cases where blood is not available, if the distribution coefficient has a CV of ≤ 25%. Therefore, the results obtained from our limited number of cases suggest that fluoxetine concentrations found in bile, skeletal muscle, brain, spleen, and heart muscle could be used with caution to estimate blood fluoxetine concentrations ranging from slightly below to slightly above therapeutic levels. Norfluoxetine distribution

Table 2. Fluoxetine concentrations obtained from 10 pilot fatalities.*

case	blood	urine	VH	bile	liver	lung	kidney	Spleen	Muscle	Brain	heart
1	0.057	—	0.005	—	2.13	1.67	0.498	1.14	0.136	0.921	0.676
2	0.196	—	—	5.76	8.16	2.27	2.52	0.361	2.48	1.47	5.76
3	1.48	0.251	—	—	—	51.9	4.85	9.75	2.15	—	5.65
4	0.263	0.385	—	2.25	7.68	13.8	1.63	5.91	0.504	2.84	2.62
5	0.682	—	—	4.44	28.6	41.7	5.34	11.1	1.77	10.3	7.81
6	0.021	0.025	—	0.126	0.691	1.56	0.204	0.403	0.056	0.316	0.227
7	0.620	—	—	5.90	—	—	8.72	18.4	—	12.1	8.26
8	0.338	0.128	0.024	3.54	7.94	19.9	1.45	5.93	0.682	3.85	2.15
9	0.362	—	—	3.01	20.7	—	1.97	7.83	0.572	4.36	2.71
10	0.280	0.250	0.038	3.03	14.2	24.0	2.96	7.44	—	5.63	—

* All concentrations shown in units of g/mL or g/g

—Specimen type not available for analysis

Table 3. Norfluoxetine concentrations obtained from 10 pilot fatalities.*

case	blood	urine	VH	bile	liver	lung	kidney	Spleen	Muscle	Brain	heart
1	0.209	—	0.018	—	12.5	7.38	1.28	4.96	0.337	4.29	1.74
2	0.571	—	—	4.09	13.9	15.1	5.78	8.21	0.880	8.32	2.76
3	0.879	0.175	—	—	—	31.9	3.42	7.5	0.751	—	2.06
4	0.691	0.754	—	4.01	16.5	41.6	4.33	13.7	1.13	8.66	4.08
5	0.054	—	—	3.80	28.0	37.9	5.45	9.81	1.59	11.3	6.39
6	0.160	0.209	—	0.783	5.83	10.2	1.02	2.78	0.338	2.32	1.63
7	0.259	—	—	1.59	—	—	3.68	6.79	—	5.67	1.54
8	0.466	0.204	0.023	4.44	15.9	37.2	2.62	5.02	1.13	7.46	3.35
9	0.450	—	—	4.01	26.6	—	3.16	12.2	0.892	10.3	2.10
10	0.357	0.268	0.031	2.60	15.4	21.4	4.52	11.6	—	6.81	—

* All concentrations shown in units of g/mL or g/g

—Specimen type not available for analysis

Table 4. Postmortem tissue distribution coefficients for fluoxetine.

	Urine/Blood	VH*/Blood	Bile/Blood	Liver/Blood	Lung/Blood	Kidney/Blood	Spleen/Blood	Muscle/Blood	Brain/Blood	Heart/Blood
n	5	3	8	8	8	10	10	8	9	9
Mean	0.9	0.10	9	38	60	9	20	2.2	15	10
s.d.	0.4	0.03	1	10	17	3	5	0.3	3	2
CV	44	30	11	26	28	33	25	14	20	20

* vitreous humor

Table 5. Postmortem tissue distribution coefficients for norfluoxetine.

	Urine/Blood	VH*/Blood	Bile/Blood	Liver/Blood	Lung/Blood	Kidney/Blood	Spleen/Blood	Muscle/Blood	Brain/Blood	Heart/Blood
n	5	3	8	8	8	10	10	8	9	9
Mean	0.8	0.07	7	42	59	9	21	2.0	18	7
s.d.	0.3	0.02	1	13	17	2	6	0.4	3	2
CV	38	29	14	31	29	22	29	20	17	29

* vitreous humor

coefficients for bile, skeletal muscle, kidney, and brain meet these criteria. While, admittedly, a study involving a greater number of samples from a larger pool of cases needs to be completed to more definitively verify these results. However, based on these findings, one could cautiously estimate a range for postmortem fluoxetine concentrations in blood.

CONCLUSION

In this study, our laboratory established the distribution of fluoxetine in various specimens from postmortem cases, with blood concentrations ranging from slightly below to slightly above therapeutic. The results obtained from these ten cases suggest that fluoxetine distribution varies widely among individuals. Calculated CV values for different tissue types ranged from 11 to 44%. However, skeletal muscle, heart muscle, brain, spleen, and bile each had a CV of ≤25%. The relatively small standard deviations associated with these distribution coefficients suggest that these specimens may be used with extreme caution to obtain an approximate blood concentration for fluoxetine.

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